

## CORRESPONDENCE



## Influenza Season and ARDS after Cardiac Surgery

**TO THE EDITOR:** A number of concurrent risk factors are associated with development of the acute respiratory distress syndrome (ARDS). One such risk factor might be asymptomatic respiratory viral infection — for example, influenza — which could prime the lungs for ARDS in patients with another overt risk factor. Patients who undergo cardiac surgery could potentially carry these viruses yet have no clinical signs or symptoms.<sup>1</sup>

In a retrospective observational cohort of 2013 patients who underwent cardiac surgery between January 2009 and January 2012, we compared the incidence of ARDS after surgery during influenza seasons (typically from December through February, when influenza is most likely to be isolated from body fluids)<sup>2</sup> with the incidence of ARDS after surgery during seasons with few, if any, influenza cases (baseline seasons). None of the patients in our study who underwent elective surgery had noted preoperative respiratory symptoms or fever in any of the seasons examined. In our analysis, the primary outcome was development of ARDS within 7 days after surgery, assessed with the use of the Berlin

criteria.<sup>3</sup> We obtained data regarding chest radiographs and the ratio between the partial pressure of arterial oxygen and the fraction of inspired oxygen ( $P_{aO_2}/F_{iO_2}$ ) through manual chart review. The secondary outcome measures were duration of mechanical ventilation, length of stay in the intensive care unit (ICU), and mortality. We added other, well-known risk factors in our multivariable model (details are provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org).

Among the 740 patients who were admitted to the ICU after cardiac surgery during baseline periods, ARDS developed in 38 (5.1%). In the periods between baseline and influenza seasons, ARDS developed in 55 of 984 patients (5.6%), and during influenza seasons, ARDS developed in 26 of 289 patients (9.0%). All cases of ARDS occurred within the first 26 hours after surgery. In our models, cardiac surgery during influenza seasons versus baseline seasons was an independent risk factor for development of ARDS (odds ratio, 1.85; 95% confidence interval, 1.06 to 3.23) (Table 1). Furthermore, the duration of mechanical ventilation was significantly longer in the influenza seasons than in baseline seasons.

In another study, involving children, no differences in postoperative length of hospital stay were found among seasons.<sup>4</sup> In addition to the use of a different end point that did not include ARDS, the definition of respiratory-virus season in that study was not based on viral identification, and the sample size was much smaller, which made the study underpowered to reveal the association that we identified. For the relationship that we found between influenza season and ARDS after cardiac surgery to be of clinical value, research is needed to determine whether perioperative strategies aimed at pre-

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**Table 1. Primary and Secondary Outcome Measures during Influenza Seasons versus Baseline Seasons.\***

Outcome	Value (95% CI)	P Value
Odds ratio for ARDS in influenza seasons vs. baseline seasons	1.85 (1.06 to 3.23)	0.03
Absolute difference in duration of mechanical ventilation between influenza seasons and baseline seasons — hr	22.64 (0.47 to 44.81)	0.05
Absolute difference in length of stay in ICU between influenza seasons and baseline seasons — hr	21.08 (–1.42 to 43.58)	0.07
Odds ratio for death in the ICU in influenza seasons vs. baseline seasons	1.57 (0.58 to 4.24)	0.37

\* Data are primary and secondary outcome measures from multivariable modeling in which age, sex, body-mass index, EuroSCORE (a preoperative risk score; scores range from 1 to 99, with higher scores indicating a higher risk of death), Acute Physiology and Chronic Health Evaluation (APACHE) IV score (a marker of illness at admission to the intensive care unit [ICU]), time in surgery, duration of cardiopulmonary bypass, units of blood products received during surgery, and season of surgery were evaluated. ARDS denotes acute respiratory distress syndrome, and CI confidence interval.

venting, detecting, or treating subclinical influenza might reduce the number of patients in whom ARDS develops.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

1. Groeneveld GH, van Paassen J, Vossen ACTM, Arbous SM, van Dissel JT. Viral infection as risk factor for acute lung injury after elective cardiac surgery? Presented at IDWeek, San Francisco, October 2–6, 2013.

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3. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307: 2526-33.

4. Spaeder MC, Carson KA, Vricella LA, Alejo DE, Holmes KW. Impact of the viral respiratory season on postoperative outcomes in children undergoing cardiac surgery. *Pediatr Cardiol* 2011;32: 801-6.

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## Preventive Therapies for Chronic Migraine

**TO THE EDITOR:** In the November 30 issue, two groups of researchers report the results of phase 3 clinical trials of drugs for the prevention of migraine. Silberstein et al.<sup>1</sup> describe the efficacy of fremanezumab, a monoclonal antibody targeting calcitonin gene-related peptide (CGRP), and Goadsby et al.<sup>2</sup> describe the efficacy of the anti-CGRP receptor erenumab. With respect to the effects of these two drugs, we note that CGRP is a potent endogenous vasodilator. Our group has been investigating the role of CGRP in vascular tone in experimental models. CGRP seems to play a larger role in altering vascular tone in rats with hypertension than in those with normotension.<sup>3,4</sup> However, in the clinical trial, no changes in hemodynamics were reported with fremanezumab, although one episode of hypertensive crisis was described. Patients who were treated with

erenumab were reported to have a slightly lower rate of hypertension than those who received placebo. We ask the authors for their view on the lack of substantial effect on blood pressure that was associated with the blockade of CGRP or its receptor. Also, do the authors have data to determine whether there were differences in treatment efficacy or safety between patients with hypertension and those without hypertension?

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